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REVIEW ARTICLE

Treating diabetic complications; from large randomized clinical trials to precision medicine

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In the last decades, many large randomized controlled trials have been conducted to assess the efficacy and safety of new interventions for the treatment of diabetic kidney disease (DKD). Unfortunately, these trials failed to demonstrate additional kidney or cardiovascular protection. One of the explanations for the failure of these trials appears to be the large variation in drug response between individual patients. All trials to date tested a drug which was targeted to a large heterogeneous population assuming that every individual will show a similar beneficial response to the drug. Post hoc analyses from the past clinical trials, however, suggest that individual patients show a marked variation in drug response. This highlights the need to personalize treatment taking proper account of the characteristics and preferences of individual patients. Transitioning to a personalized therapy approach will have implications for clinical trial designs, drug registration and its use in clinical practice. Successful implementation of personalized medicine thus requires engagement of multiple stakeholders including academic community, pharmaceutical industry, regulatory agencies, health policy makers, physicians and patients. This supplement of *Diabetes Obesity and Metabolism* provides a summary on the state-of-the-art of personalized medicine in diabetic kidney disease from the views of various stakeholders.

KEYWORDS

chronic kidney disease, clinical trials, diabetes, drug development, personalized medicine

The prevalence of type 2 diabetes is continuously increasing. Patients with type 2 diabetes face a high risk of progressive renal function loss and cardiovascular (CV) disease. The current guideline recommended treatments target multiple risk factors like glucose, blood pressure, cholesterol, body weight, smoking, albuminuria in order to reduce the risk of renal and CV complications. Intervention in the renin-angiotensin-aldosterone-system renin-angiotensin-aldosterone-system (RAAS) with drugs that inhibited the angiotensin-receptor blockade (ARB) advanced pharmacotherapy in patients with type 2 diabetes and chronic kidney disease. The RENAAL and IDNT trials showed that losartan and irbesartan, respectively, reduced renal risk in this population.^{1,2} However, despite the success, the residual risk remains high.

Since the introduction of ARBs for renal protection, many attempts have been made to further lower renal and CV morbidity by either more stringently inhibiting the RAAS using dual RAAS blockade (angiotensin converting enzyme inhibitors [ACEi] + ARB in the VA

NEPHRON-D trial or ARB + direct renin inhibition in the ALTITUDE trial),^{3,4} or targeting new risk markers like albuminuria (sulodexide in the SUN trial),⁵ hemoglobin (erythropoietin stimulation agent in the TREAT trial), endothelin-1 (endothelin receptor antagonist in the ASCEND and SONAR trials)^{6,7} or inflammation and oxidative stress (bardoxolone, in the BEACON trial).⁸ Unfortunately, all these strategies did not result in further renal or CV protection, and sometimes even resulted in increased risk.

The failure of these trials can be attributed to multiple factors. Two important factors are, first, a between patient variability in reduction of the intermediate risk factors (eg, variation in the degree in blood pressure or albuminuria responses between patients). Second, it appears that all drugs induced changes in other renal or CV risk markers (eg, rise in serum potassium and or rise in sodium retention).

Indeed, post hoc analyses of recent trials showed a large variation in the individual response in the targeted risk marker. For example, in

the ALTITUDE trial, a large variation in the albuminuria response to aliskiren was observed (interquartile range -49% to $+42\%$).⁹ Patients with a more than 30% reduction in albuminuria were at a 50% lower risk compared to placebo-treated patients in whom albuminuria did not change. This suggests that if the clinical trial population was selected more carefully before starting the trial by selecting only those individuals with a reduction in albuminuria the outcome of the trial may have been completely different. Another example comes from the BEACON trial. The BEACON trial tested the efficacy of the antioxidant anti-inflammatory agent bardoxolone methyl. The trial was terminated early due to excess heart failure in the bardoxolone methyl treatment arm most likely due to sodium/fluid retention induced by the drug.⁸ A post-hoc analysis of the trial indicated that if patients would have been selected who are not sensitive for the sodium retaining effects of the drug, the increased risk for heart failure that was associated with bardoxolone therapy might have been avoided.¹⁰ This would have led to the possibility to characterize the effect of the drug on renal outcomes more precisely and may have resulted in a positive outcome of the trial.

The lesson learned from these past trials and their post-hoc analyses is that we should select clinical trial participants more carefully with particular emphasis on the individual variability in the drug response of several risk factors to the new intervention: patients with "bad" responses should be excluded from trials and patients with "good" responses should be included. This resembles very much current clinical practice in which personalized medicine is more and more practiced aiming to individualize therapy for each patient.

New trials are indeed going into the direction of personalized medicine. The SONAR trial is one example. The trial uses an active enrichment design in which all patients are exposed for 6 weeks to the tested endothelin receptor antagonist atrasentan.^{7,11} Patients who had more than 30% albuminuria reduction during the 6 weeks active enrichment period will be randomly assigned for long-term treatment to atrasentan or placebo. Patients who showed excess sodium retention, measured by a gain in body weight or B-type natriuretic peptide, to atrasentan exposure are excluded from the trial. This way the trial population is enriched for patients who are likely benefit. The enrichment approach applied in SONAR mimics clinical practice where the response is monitored after drug initiation and in case of lack of response or side effects the dose of the drug is down-titrated or discontinued altogether. The SONAR trial was discontinued earlier due to a lower than anticipated event rate.^{7,11} The impact of the enrichment design element on the event rate remains to be seen.

Past clinical trials in diabetic kidney disease has shown that an increased attention how individual patients respond to drugs is needed to improve pharmacotherapy and outcomes of patients. To personalize pharmacotherapy, drug development and drug use in clinical practice for diabetes kidney disease should be an integrated undertaking of healthcare providers, the academic community, the pharmaceutical industry, trial designers, health policy makers, regulatory authorities, insurance companies, doctors, patients and the general public. Early engagement of these stakeholders is important as they may have different priorities. A conference on personalized medicine in diabetic kidney disease was held in December 2017 in Groningen, the Netherlands to discuss the state of the art, challenges and

solutions for successful implementation of personalized medicine in diabetic kidney disease. This supplement of *Diabetes Obesity and Metabolism* provides a summary of what was discussed.

A large number of novel biomarkers for diabetic kidney disease emerged in the past decade. These biomarkers typically address one specific mechanisms of disease such as inflammation, fibrosis or endothelial function. Since diabetic kidney disease is a heterogeneous disease biomarker combination which represents different molecular processes implicated in the progression of diabetic kidney disease (DKD) may be particularly useful to better phenotype individual patients and response to interventions in the future. Mulder et al describe in this supplement of *Diabetes Obesity and Metabolism* how systems biology approaches and bio-informatic tools can be used to achieve this goal.¹²

A substantial proportion of patients do not respond to guideline recommended therapies or new therapies. Enriching clinical trials for patients who respond to the investigational drug, as done in the SONAR trial, directly raises the question what alternative strategies are available for non-responder patients. New trial designs methodologies, like platform design may be a next step to advance enrichment designs and offer alternative interventions for non-responsive patients. As described by Heerspink et al in this supplement, platform designs support the simultaneous conduct of multiple trials in several related diseases with different interventions using the same infrastructure.¹³ Within a platform non-responder patients can theoretically move on to a new intervention depending whether they responded to the assigned therapy. The statistical elements for such design require additional consideration but the platform clearly offers an opportunity to define an optimal trial population for each new drug.

Implementation of precision medicine involves support from many stakeholders including regulators, patients, physicians and patients. For example, regulatory agencies should develop models to assess efficacy and safety and market drugs for specific targeted patient populations and healthcare providers/physicians have to develop new guidelines and implement precision medicine in clinical practice. Most importantly, patients and patient organizations have to be involved as they are the end-users and should ultimately benefit from an individualized therapy approach. The perspectives of these stakeholders are described in the articles by Mol et al and De Vries et al in this issue.^{14,15}

The treatment of diabetes and diabetic kidney disease as well as many other chronic diseases has been characterized by a one size fits all approach. However, recent experiences have taught us that this approach is no longer sustainable. Examples from the oncology area where personalized medicine has driven progress for years illustrate that it is time to change current model of drug development and drug use in clinical practice. Thus, we are up for a change from "one drug fits all" into the new era of "a fit for each size."

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Conflict of interest

H.J.L.H. is a consultant for Astellas, Abbvie, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen and Merck and reports research grants from AstraZeneca, Boehringer Ingelheim and Janssen. He has a policy that all honoraria are paid to University Medical Center, Groningen, the Netherlands. D.d.Z. is a consultant for, and receives honoraria (to employer) from, AbbVie, Astellas, Bayer, Boehringer Ingelheim, Fresenius, Janssen and Mitsubishi-Tanabe.

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